REMARKS

Entry of the foregoing and favorable reconsideration and reexamination of the subject application, as amended, pursuant to and consistent with 37 C.F.R. § 1.112, and in light of the remarks which follow, are respectfully requested.

By the present amendment, Claim 15 has been amended the recite "the" in front of the several promoters which have been claimed in lieu of "a", as suggested by the Examiner. Applicants submit that no new matter has been added via this amendment.

Claim for Priority Under 35 U.S.C. § 119

Applicants note that the Examiner has indicated that the certified copy of the priority document has not been received. That the certified copy of the priority document was submitted on September 27, 2000. Our records indicate the priority document was received by the Patent Office on October 2, 2000. Please acknowledge receipt of the certified copy of the priority document.

35 U.S.C. § 103(a)

Claims 15, 18 and 19 have been rejected under 35 U.S.C. § 103(a) as being unpatentable over Perricaudet et al. in view of Quantin et al. and Rice et al. For the following reasons, this rejection is respectfully traversed.

Perricaudet et al. teach the ability of a recombinant adenovirus to infect skeletal muscle cells. The recombinant adenovirus was constructed by replacing the internal E1 region of the adenoviral genome by a recombinant expression promoter driven by the adenorial major late promoter as depicted in Figure 2. Intramuscular injection into mice of a β-galactosidase encoding adenovirus resulted in substantial expression of the transduced β-galactosidase gene several days post infection. Perricaudet et al. fail to mention that other promoters such as the ones set forth in the claims and especially the promoter from the RSV LTR can be used to express heterologous genes in muscle cells.

Quantin et al. teach an E1- and E3 deleted adenovirus expressing the β-galactosidase gene under the control of a mouse skeletal α-actin promoter reinforced by an enhancer from a mouse myosin light chain gene which is muscle specific. β-galactosidase expression was obtained in infected myogenic cultured cells and fused myoblast cultures as well as in mice muscles after intramuscular injection. Quantin et al. disclose that the muscle-specific sequences used in the context of β-galactosidase gene expression should be suitable to direct expression of

sequences encoding (mini)dystrophin in muscles. Quantin et al. fail to mention that other promoters such as the ones set forth in the claims and especially the promoter from the RSV LTR can be used to express heterologous genes in muscle cells.

Rice et al. is directed to a study of transcriptional regulation of HIV-1 by the tat gene product in HeLA cells. The references discloses an l E-1 deleted adenoviral containing in place of the E1 sequences the RSV LTR fused to the cat gene for use as a control in the study. This vector was constructed as a control since the RSV LTR was known to be insensitive to tat. Cat activity was equivalently detected after infection of tat-expressing HeLA cells and the parental HeLA cells with the adenoviral RSV containing vector.

It should be emphasized, however, that HeLA cells are epithelial-like cells obtained from human cervical adenocarcinoma. HeLA cells cannot be equated with muscle cells and hence there is no guidance and no expectation of success that the RSV LTR promoter can be used for expression of an adenovirus-carried transgene in muscle cells. Furthermore, it should also be noted that Rice et al. do not describe the RSV LTR promoter as being a strong promoter as the Examiner purports.

In addition, one of skill in the art would not be motivated to combine the teachings of the Rice et al. reference with that of Quantin et al. and/or Perricaudet et al. This reference is directed to expression in a different cell type and for an unrelated purpose. There is no teaching or suggestion that the RSV LTR promoter can or should be used in other cell types, much less muscle cells, for expression of heterologous genes.

Thus, the cited references taken alone or in combination would not motivate the skilled artisan to use the RSV promoter in an adenoviral construct for expression in muscle cells. There was simply no expectation of success that this promoter could in fact work.

Therefore, in view of the above, withdrawal of this rejection is respectfully requested.

Claim 17 has been rejected under 35 U.S.C. § 103(a) as being obvious over Perricaudet et al. in view of Rice et al. and Nabel et al. For the following reasons, this rejection is respectfully traversed.

Claim 17 is directed to a composition comprising a replication-defective adenoviral vector expressing a thrombolytic polypeptide and depends from Claim 15 reciting specific promoters.

As discussed above, Perricaudet fail to disclose the presently claimed promoters. Indeed, the promoters that are disclosed are adenoviral major late promoters. As discussed previously, Rice et al. is silent with using the recombinant construct including the RSV LTR promoter in muscle cells. It should also be noted that Rice et al. is silent with respect to the fact that the RSV LTR is a strong promoter.

Nabel et al. is directed to the transformation of cells on the wall of a blood vessel or in an organ through catheter delivery to cause expression of various polypeptides. It should be brought to the attention of the Examiner that there are actually two different embodiments disclosed in Nabel et al., as indicated in the Headings. The only embodiment of introducing viral vectors is set forth at column 7, line 52 to column 8, line 69 as evidenced by the heading: "B. Introduction of recombinant genes directly into cells on the wall of a blood vessel or perfused by a specific circulation *in vivo;* infection or transfection of cells on the vessel wall and organs."

There is simply no disclosure in this section that a defective adenoviral vector can be expressed in muscle cells. Moreover, there is no description of the specifically claimed promoters for expression of any genes in muscle cells including a thrombolytic agent.

Based on the specification's disclosure and the experimental results provided in Nabel et al., it is clear that expression of the therapeutic gene is targeted in endothelial cells lining the blood vessels as indicated:

(1) at column 15, lines 43 to 45, where it is stated that "it is preferred that the cells caused to express the exogenous therapeutic agent protein be endothelial cells";

(2) at column 16, lines 52 to 54, where it is disclosed that "Light microscopy documented β-galactosidase staining primarily in endothelial cells of the intima in experimentally seeded vessels," and

(3) at column 16, lines 65 to 69, where it is stated that "In instances of thrombus formation, β-galactosidase staining was seen in endothelial cells extending from the vessel wall to the surface of the thrombus."

Moreover, it should also be noted that in Nabel et al. the passages concerning systemic delivery of a recombinant vector there is simply no teaching that the vector used is defective and the therapeutic gene is under the control of a promoter as claimed by applicants.

In conclusion, Nabel et al. does not disclose:

(1) a defective recombinant adenoviral vector for gene transfer in muscle cells;

(2) wherein said defective recombinant vector is under the control of a promoter that is currently recited in the claims; and

(3) the expression is achieved in muscle cells.

Therefore, given the teachings of the prior art, one of ordinary skill in the art at the time the invention was made would not be motivated to use the specified promoters to drive expression of an heterologous gene in muscle cells.

Therefore, in view of the above, withdrawal of this rejection is respectfully requested.

Obviousness-Type Double Patenting

Claims 15 and 17 to 19 have been rejected under the judicially created doctrine of obviousness-type double patenting. Applicants request that this rejection be held in abeyance until there is allowable subject matter. At that time, Applicants will proceed by filing a Terminal Disclaimer, if appropriate.

35 U.S.C. § 112, Second Paragraph

Claims 15 and 17 to 19 have been rejected under 35 U.S.C. § 112, second paragraph. Claim 15 has been amended as suggested by the Examiner rendering this rejection now moot. Applicants respectfully request withdrawal of the rejection.

From the foregoing, favorable action in the form of a Notice of Allowance is respectfully requested and earnestly solicited.

Respectfully submitted,

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MARKED UP-VERSION TO SHOW CHANGES MADE

15. (Thrice Amended) A composition comprising (i) a non replicative recombinant adenoviral vector wherein said non replicative recombinant adenoviral vector comprises a heterologous polynucleotide sequence encoding a polypeptide, which polynucleotide sequence is inserted into a deleted E1 region of said non replicative recombinant adenoviral vector and is under the control of a promoter selected from [a] the promoter contained in the Long Terminal Repat of Rous Sarcoma Virus, [a] the promoter of the IE gene of cytomegalovirus, [a] the Mouse Mammary Tumor Virus inducible promoter and [a] the metallothionine promoter wherein said polypeptide is expressed in said muscle cells and (ii) a pharmaceutically acceptable carrier.